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Molecular Dynamics in Amorphous Ergocalciferol

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Abstract. While developing new pharmaceutical products based on drug substances in their amorphous form, the molecular mobility of amorphous active ingredients have to be characterized in detail. The molecular mobility in the supercooled liquid and glassy states of ergocalciferol is studied using broadband dielectric spectroscopy over wide frequency and temperature ranges. Dielectric studies revealed a number of relaxation process of different molecular origin.

Keywords: Amorphous pharmaceuticals, Broadband dielectric spectroscopy, Molecular dynamics, Glass transition.
PACS: 77.22.Gm, 64.70.P-

INTRODUCTION

When a liquid is cooled avoiding crystallization, we get supercooled liquid and on further decrease of temperature a glassy state can be reached. At glass transition temperature T_g, molecular motions slow down to the time scale of the order of few hundreds of seconds. Below T_g, the molecular rearrangement is extremely slow and the molecules cannot reach their equilibrium condition. Relaxation dynamic studies provide detailed information about molecular mobility above and below T_g. Amorphous Pharmaceuticals have greater solubility and dissolution rate than their crystalline counterpart [1]. Molecular mobility of the amorphous state forms a key factor responsible for the physical and chemical stability of the active pharmaceutical ingredient (API). Thus, understanding the nature and molecular mechanism responsible for the secondary relaxations observed in the glassy state is very crucial to ascertain the shelf life of these APIs. One of the best tools available to investigate the relaxation properties of the amorphous materials is the broadband dielectric spectroscopy (BDS) since it provides information about molecular dynamics in liquid and glassy states over a wide range of frequency, temperature and even at elevated pressures.

EXPERIMENTAL

Ergocalciferol with purity ≥ 98% was purchased from Sigma Aldrich, USA and used as received without further purification. It is stable against crystallization throughout the experiment. Glassy ergocalciferol was prepared by cooling the melt by exposing very high cooling rate to avoid crystallization. Dielectric measurements were carried out using Novocontrol Alpha analyzer in the frequency range of 10 mHz – 10 MHz. The temperature is controlled using dry nitrogen-flow in the Novocontrol Quatro cryosystem (-170°C – 125°C). The sample was heated to few degrees above the melting point cooled rapidly to -170^0C. Dielectric spectra were measured isothermally, after stabilizing the temperature.

RESULTS AND DISCUSSIONS

The chemical formula of ergocalciferol is ($C_{28}H_{44}O$) with a molecular weight of 396.65g/mol and melting point ranges between 114°C –118°C. The chemical structure of ergocalciferol is given below.

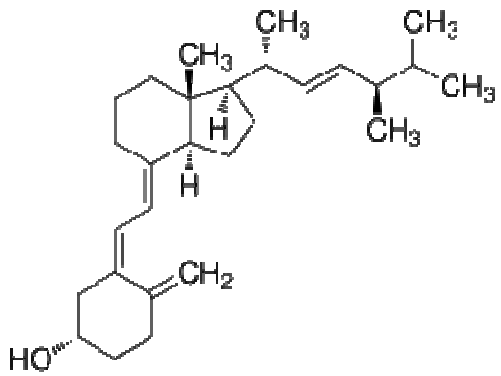

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FIGURE 1. Chemical structure of ergocalciferol.

The sample was earlier studied by Fukuoka *et.al* with DSC and they reported T_g as 290 K, T_m =376 K and T_g/T_m = 0.77 [2]. From the dielectric studies we got T_g as 291 K. Temperature variation of dielectric loss ε'' at 10 Hz, 100 Hz, 1 kHz, 10 kHz, and 100 kHz test frequencies is shown in Fig. 2.

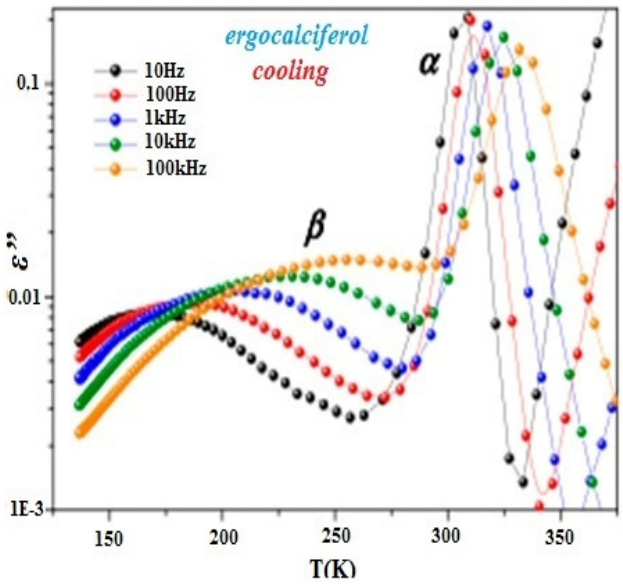

FIGURE 2. Variation of ε'' with temperature.

Two clear and distinct relaxation processes represented as α-process which freezes at T_g and β-process which survives even below T_g have been shown in the figure. According to microscopic view, two different mechanisms can be attributed to the secondary processes, one due to the motions of molecular subunits that can relax independently from the whole molecules (intra-molecular origin), while the other due to the rotations of the entire molecule. The former is expected in all the flexible polymers and low molecular liquids, while the later is often hindered and has been considered to be the intrinsic property of glass forming systems of all kinds after the pioneering discovery by Johari and Goldstein via rigid dipolar glass formers in 1970.The increase in loss at higher temperatures above α-process is due to conductivity which increases with temperature in an Arrhenius fashion. The variation of dielectric permittivity ε' for the same test frequencies is shown in Fig. 3.

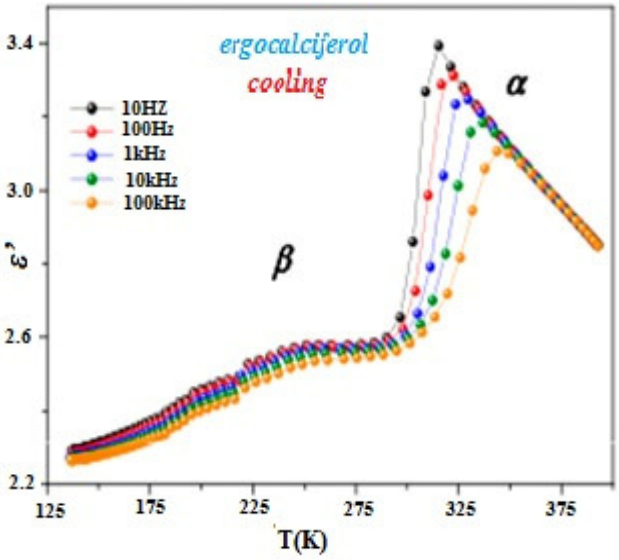

FIGURE 3. Variation of ε' with temperature.

From the Fig. 3 it is clear that the dielectric strength increases on decreasing temperature in 1/T behavior and the isothermal spectra is showing Cole-Davidson behavior and ε_∞ tends to reach the high frequency limit of the dielectric permittivity of 1.05 n_D^2 within the experimental uncertainty. This trend can be easily being seen upto the liquid region with a slight decrease of slope around 1.3-1.4 T_g as represented as liquid-liquid transition by some researchers. The structural relaxation peaks of both loss and permittivity are rapidly shifting to high frequencies on increasing the temperature in a non-Arrhenius behavior and the data can be described by the Vogel-Fulchers-Tammanns equation given by

$$f_{m,\alpha} = f_{0,\alpha} e^{\left(\frac{-B}{(T-T_0)}\right)}. \qquad (1)$$

Where T_0 is the limiting temperature, $f_{0,\alpha}$ is a constant and B=E/R, where E corresponds to the activation energy. The parameters of the above equation are log f_0(Hz) = 14.99 and B =2245.75 and T_0 =236.33 K. From the VFT fit we got T_g= 291.16 K, activation energy for α- process, E_α = 18.67 kJ/mol and the fragility index m = 94.46. The strength of the β-relaxation decreases on decreasing temperature in a monotonous manner which is reflected in the dielectric loss map in Fig. 2. The isothermal spectra often symmetrical and shows Cole-Cole (CC) behavior, which moves slowly to lower frequencies on decreasing temperature. The symmetric spectral shape function (CC) often shows a value greater than 0.5 which is expected for secondary relaxations. The f_m

values of β- process is analyzed using the Arrhenius equation given by

$$f_m = f_0 e^{\left(\frac{-E}{RT}\right)}. \qquad (2)$$

Where E is the corresponding activation energy and f_0 is the pre-exponential factor. The corresponding values are $\log f_{0,\beta} = 13.32$, $E_\beta = 37.48$ kJ/mol.

CONCLUSIONS

Dielectric studies revealed a number of relaxation process of different molecular origin. From the structural information of the molecule, it is clear that there is no intramolecular degrees of freedom apart from the trivial motions associated with rotations of the $-CH_3$ groups etc. Hence the resolved secondary relaxation is from the JG relaxation. In addition to these, there exist a correlation between the breadth of the α–relaxation and the position of the β–relaxation of ergocalciferol as per the coupling model predictions, and we infer that the resolved secondary relaxation is due to the JG relaxation.

REFERENCES

1. Murdande, S. B, Pikal, M. J, Shanker, M, Bogner, R. H, *Pharm.Res*, Springer, 2010, pp. 2704-2714.
2. E. Fukuoka, M. Makita, Y. Nakamura, *Chem. Pharm. Bull*, 1047-1050(1989).